

REMARKS

Claims 1-43 are pending and under examination in this application. Claims 35, 38 and 43 have been corrected to remove the inadvertent double numbering. Claim 39 has been cancelled without prejudice as being duplicative with claim 10. Accordingly, the corrections and amendment do not raise an issue of new matter and entry thereof is respectfully requested. Applicant has reviewed all grounds of rejection and respectfully traverse for the reasons that follow.

Priority

The Office has accorded priority for the immobilization of enzymes that generate a signal from pyrophosphate to U.S. provisional application serial no. 60/160,927, filed October 22, 1997.

Applicants submit that the claimed invention should be accorded priority to all of the applications listed in the priority claim because support for the claimed invention can be found throughout these applications as filed. The brief statement in the Office Action fails to support the Office's conclusion. Accordingly, Applicants respectfully request priority be accorded all applications to which the benefit of priority has been claimed.

Claim Interpretation

The Office construes the claim term "covalently attached" to include both covalent bonds and non-covalent bonds. In this regard, the Office cites to the definition of the term which recites that two moieties are attached by at least one bond, but then references descriptions of multimeric complexes being encompassed within the meaning of the term.

Applicants respectfully submit that the Office's interpretation misconstrues the meaning of the term. The term "covalent" is defined and used in the application according to its ordinary meaning in the art. As pointed out by the Office, the specification defines the term "covalently attached" as referring to two moieties being attached by at least one bond including sigma bonds, pi bonds and coordination bonds. References to covalent attachment of multimeric complexes such as hybridization complexes do not change the meaning of this term. Covalent attachment of

one moiety within a multimeric complex to another moiety such as a surface means that the referenced moiety within the multimeric complex is covalently attached. It does not mean that all moieties within a multimeric complex are covalently attached. For example, the passages cited by the Office reference the capture probe as being covalently attached to a surface or a microsphere. Hence, the other components, which can be non-covalently attached to the capture probe, are not referred to, or required to be, covalently attached to the surface or the microsphere. Accordingly, the term “covalently attached” as it is defined and used in the application should be accorded its ordinary meaning in the art.

Rejections Under 35 U.S.C. § 103

Claims 1-16, 22-27 and 31-42 stand rejected under 35 U.S.C. § 103(a) as being obvious over Rothberg et al., U.S. Patent No. 6,274,320, in view of Walt et al., U.S. Patent No. 6,327,410. The Office alleges that Rothberg et al. describe a method of sequencing that contains the steps recited in independent claims 1, 10 and 34 except for the use of microspheres on the surface of a fiber optic bundle. Walt et al. is cited for describing this missing element. The Office concludes that it would have been obvious to one skilled in the art to use the microspheres of Walt et al. distributed over the surface of a fiber optic sensor in the sequencing method of Rothberg et al. allegedly because Walt et al. states that microspheres allow generation of large fiber optic arrays and because bead-based chemistry systems combined with the use of a substrate allows synthesis of bioactive agents to be separated from their placement on an array.

The invention is directed to a method of sequencing a plurality of target nucleic acids. The method includes providing an array having a substrate with discrete sites, a population of microspheres having at least first and second subpopulations and an enzyme for generating a pyrophosphate signal attached at the discrete sites. Providing first and second hybridization complexes containing first and second target sequences attached to first and second subpopulations, respectively. Simultaneously extending the first and second primers, and detecting the release of pyrophosphate (PPi) with the enzyme attached at the discrete sites within a common reaction chamber of the simultaneous extensions to determine the sequence of the plurality of target nucleic acids.

Where an invention is contended to be obvious based upon a combination of elements across different references, the Federal Circuit case law “require that there be a suggestion, motivation or teaching to those skilled in the art for such a combination.” *Iron Grip Barbell, Co. v. York Barbell, Co.*, Case No. 04-1149, slip op. at 5 (Fed. Cir. December 14, 2004) (citing *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988)). This requirement prevents the use of “the inventor’s disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight.” *Id.* Further, obviousness can be rebutted where it is shown that the prior art taught away from the claimed invention. *Iron Grip Barbell, Co.* Case No. 04-1149, slip op. at 7 (citing *In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997)).

Applicants respectfully submit that the cited combination of references fail to teach, suggest or motivate those skilled in the art to combine elements of the method of the invention as they are claimed. In particular, Rothberg et al. teaches away from any teaching, suggestion or motivation to combine the sequencing method described therein with the microsphere containing array described by Walt et al. For example, Rothberg et al. explicitly point to reported problems associated with the use of pyrophosphate sequencing in combination with a solid support such as beads. Rothberg et al. characterize the pyrophosphate sequencing method of Ronaghi et al. as being undesirable when Rothberg et al. state:

In these early studies, sequencing of a PCR product using streptavidin-coated magnetic beads as a solid support was presented. However, it was found that the loss of the beads during washing, which was performed between each nucleotide and enzyme addition, was the limiting factor to sequence longer stretches.

Column 21, lines 14-34.

Other descriptions in Rothberg et al. fail to counter the above characterization of the pitfalls associated with combining pyrophosphate sequencing with beads. Rather, Rothberg et al. provides a detailed section entitled “Mathematical Analysis Underlying Optimization of the Pyrophosphate Sequencing Reaction” that sets forth various theories and calculations why his sequencing strategy is likely possible (beginning at column 21, line 11). Following mention of the drawbacks and limitations of the method of Ronaghi et al., the descriptions in Rothberg et al. appear to consider molecular and thermodynamic mechanisms involved in the pyrophosphate sequencing methods described therein, none of which describe or suggest combining any

pyrophosphate sequencing method with microspheres. Rather, the descriptions in Rothberg et al. are directed to a method of carrying out reactions using nucleic acid templates and other reagents in a configuration that minimizes diffusion of pyrophosphate between different nucleic acid templates. Beads are not suggested as providing the advantages of minimizing diffusion in the sequencing strategy of Rothberg et al. According to Rothberg et al., the combination of pyrophosphate sequencing with microspheres was undesirable, limited and inapplicable to pyrophosphate sequencing strategies. These descriptions in Rothberg et al. teach away from the asserted combination of Rothberg et al. and Walt et al. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Claims 18, 19, 28-30 and 43 stand rejected under 35 U.S.C. § 103(a) as being obvious over Rothberg et al., Walt et al., Nyren et al., WO 98/13523, and the Stratagene catalog (1998, p39). Rothberg et al. and Walt et al. are applied as described above. Nyren et al. is cited allegedly for describing pyrophosphate sequencing kits whereas the Stratagene catalog is cited for allegedly providing a motivation to combine reagents into a kit format to arrive at the claimed invention.

Applicants respectfully point out that the kit of claim 18 includes a substrate with a surface having discrete sites and a population of microspheres distributed on the sites. As pointed out above, Rothberg et al. teach away from combining microspheres with a pyrophosphate sequencing method. Therefore, any motivation to combine these elements of the claimed kit must come from the tertiary references and outweigh the teaching away found in Rothberg et al. However, neither Nyren et al. or the Stratagene catalog provide the requisite motivation. Accordingly, any description of a kit having different sets of sequencing reaction components fails to provide a desirability to combine the elements of the primary and secondary references. In addition, the mere citation of kits also fails to outweigh the teaching away found in Rothberg et al. from combining pyrophosphate sequencing with beads. Absent such a teaching, suggestion or motivation to combine that outweighs Rothberg et al.'s rebuttal of obviousness, the invention as claimed is not rendered obvious over the cited references and withdrawal of this ground of rejection is respectfully requested.

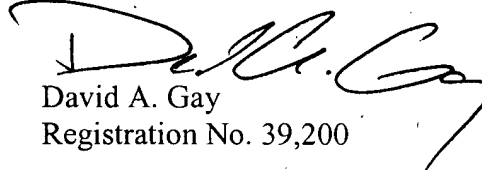
CONCLUSION

In light of the Amendments and Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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